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# General Trends in Reaction of *N*-Aryl-3-oxobutanethioamides with 2-Aminoazoles(Azines)

**V. N. Britsun, A. N. Borisevich, and M. O. Lozinskii**

*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev, 02660 Ukraine*
*e-mail: bvn1967@rambler.ru*

Received July 18, 2006; final version May 30, 2007

**Abstract**—Reaction products obtained from *N*-aryl-3-oxobutanethioamides and 2-aminoazoles(azines) are derivatives of (arylamino)pyrimidines and pyrimidinethiones. The ratio of the products depends on the basicity of 1,3-binucleophiles, acidity of the medium, and the character of substituents in the phenyl ring of initial thioamides.

**DOI:** 10.1134/S1070428007100247

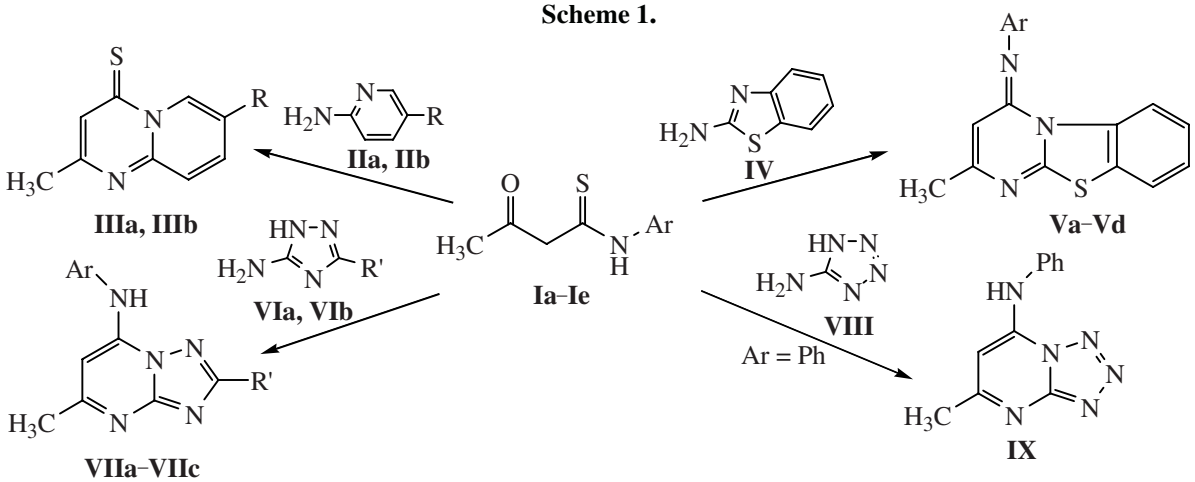
We showed recently that *N*-aryl-3-oxobutanethioamides react with 1,3-binucleophiles like 3-amino-5-R-1,2,4-triazoles [1], 2-amino-5-R-pyridines [2], 2-aminothiazoles [3], and guanidine carbonate [4] to form two groups of compounds: derivatives of pyrimidine-4-thione and 4-(arylamino)-pyrimidine, whose ratio is affected by the basicity of 1,3-binucleophiles and by the character of substituents in the phenyl ring of initial butanethioamides [1–4].

Although the majority of the reactions save those described in [4] were carried out in AcOH the role of the latter was not investigated. Still, the condensations with an acyclic 1,3-binucleophile, guanidine, occurred also without a proton-donor solvents [4].

The target of the present study was investigation of the solvent effect (AcOH and $CF_3COOH$) on the direction of reaction between *N*-aryl-3-oxobutanethioamides and 2-aminoazoles(azines), and also analysis and systematization of previously obtained results [1–4] and revealing the general trends in the mentioned transformations.

*N*-Aryl-3-oxobutanethioamides **Ia–Ie** at 100–105°C reacted with 2-amino-5-R-pyridines **IIa** and **IIb**, 2-aminobenzothiazole (**IV**), 3-amino-5-R-1,2,4-triazoles **VIa** and **VIb**, and 5-aminotetrazole (**VIII**) also in the absence of the protonic solvents to give 4*H*-pyrido[1,2-*a*]pyrimidine-4-thiones **IIIa** and **IIIb**, 4-arylimino-4*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidines **Va–Vd**, 5-arylamino-1,2,4-triazolo[1,5-*a*]pyrimidines **VIIa–VIIc**, and

**Scheme 1.**




Ar = Ph (**Ia, Va, VIIa, IX**), 4-$MeOC_6H_4$ (**Ib, Vb**), 4-$MeC_6H_4$ (**Ic, Vc**), 3-$CF_3C_6H_4$ (**Id, Vd, VIIb**), 3-$ClC_6H_4$ (**Ie, VIIc**); R = H (IIa, **IIIa**), Me (**IIb, IIIb**); R' = H (**VIa, VIIa**), SMe (**VIb, VIIb, VIIc**).

5-phenylaminotetrazolo[1,5-*a*]pyrimidine (**IX**), whose structure and composition were proved by $^1$H NMR spectra and elemental analyses (Scheme 1).

The variation of the ratio of the reaction products as a function of aminoazoles(azines) basicity, solvent acidity, and the character of the substituents in the phenyl ring of oxobutanethioamides is presented in Tables 1 and 2.

In contrast to reactions in acetic acid the cyclocondensations in the absence of the protonizing solvents occurred selectively giving as a rule fused derivatives of 4-(arylimino)pyrimidinre.

As expected no dependence existed of the ratio 4-(arylamino)pyrimidine:pyrimidine-4-thione on p$K_\alpha$ of initial 2-aminoazoles(azines) (Table 1). However the variation in the ratio of the products correlates not with p$K_\alpha$ of 2-aminoazoles(azines) but with those of the corresponding unsubstituted azoles(azines). This fact is due to reaction of *N*-aryl-3-oxobutanethioamides with 1,3-binucleophiles proceeding through enthioamide **A** [4] (Scheme 2) where the basicity of the enamine nitrogen is diminished and therefore the intramolecular cyclization is governed by the basicity of the endocyclic nitrogen.

The data of Tables 1 and 2 unambiguously show that the protonizing solvent (AcOH) also significantly affects the reaction direction. At the use of $CF_3COOH$ no cyclocondensation occurred of *N*-aryl-3-oxobutanethioamides with 2-aminoazoles. Apparently this is due to the fact that $CF_3COOH$ being a strong acid (p$K_\alpha$ 0.23 [5]) completely protonates the amino group of 2-aminoazoles

**Table 1.** Ratio of products of reaction between *N*-phenyl-3-oxobutanethioamide (**Ia**) and 2-aminoazoles(azines) at 100–105°C

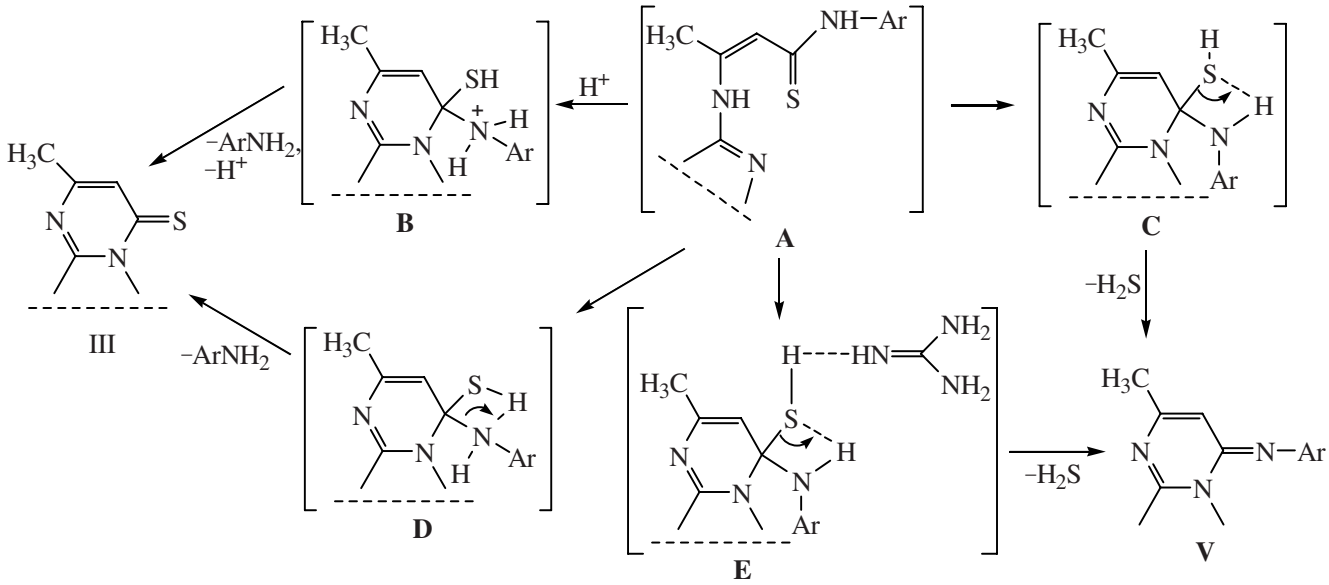
| Compound | p$K_\alpha$ [9, 10] | Ratio (%) arylimine:thione (AcOH) | Ratio (%) arylimine:thione (without solvent) |
|---|---|---|---|
| Guanidine | 13.71 | – | 28:0 [1–4] |
| 2-Amino-pyridine (pyridine) | 6.86 (5.23) | 0:65 | 0:47 |
| 3-Amino-1,2,4-triazole 1,2,4-triazole) | 4.17 (2.55) | 8:50 | 62:0 |
| 2-Aminothi-azole(thiazole) | 5.39 (2.53) | 35:30 | – |
| 2-Aminobenzo-thiazole(benzoth iazole) | 4.51 (1.2) | 62:16 | 59:0[a] |
| 5-Aminotetra-zole (tetrazole) | 1.82 (–2.68) | – | 56:0 |

[a] The ratio in toluene was 64:0.

**Table 2.** Ratio of products of condensation of *N*-aryl-3-oxobutanethioamides **Ia, Ib**, and **Id** with 2-aminobenzothiazole (**IV**) at 100–105°C

| Solvent | Ratio (arylimino)pyrimidine:pyrimidinethione (%) | | |
|---|---|---|---|
| | Ar = Ph | Ar = 4-$MeOC_6H_4$ | Ar = 3-$CF_3C_6H_4$ |
| ACOH | 62:16 | 32:34 | 59:0 |
| Without solvent | 59:0 | 48:0 | 55:0 |

**Scheme 2.**



thus preventing their reaction with 3-oxobutanethioamides.

The data of Tables 1 and 2 suggest that two groups of competing reactions occur. The reactions should be regarded both from the thermodynamic and from electronic viewpoints. It is known [6] that C–N bond is by 13 kJ mol$^{-1}$ more stable than C–S bond (energies of formation are respectively 285 and 272 kJ mol$^{-1}$). However to estimate the possibility of a certain process to occur it is necessary to take into account the energy effects of all accompanying phenomena. In the case in question the reaction products and the solvent possess either basic or acidic properties, and therefore the neutralization (protonation) enthalpy also should be considered; it amounts to 13.3 kJ mol$^{-1}$ [7]. Inasmuch as the nucleo-philic substitution at a carbon bonded with a double bond to oxygen or sulfur proceeds by a tetrahedral mechanism [8] the neutralization processes should favor those reactions of highly basic 2-aminoazoles(azines) in acetic acid which involve the elimination of arylamines and the formation of pyrimidinethiones. Actually, the higher the basicity of the initial heterocycle, the higher was the yield of thione in cyclocondensations performed in AcOH (Table 1). In all likelihood pyrimidinethiones **III** formation occurred via intermediate **B** where the arylamine elimination was easy.

Since intermediate **B** contained three nitrogen atoms it should be revealed which among them suffered protonation more likely. It should be also kept in mind that in intermediates **B**–**E** the nitrogen of the arylamino group is outside the pyrimidine ring plane, i.e., it is not in conjugation with the ring. Therefore the pyrimidine ring decreases the electron density on the N atom of the arylamino group only by the inductive effect. The basicity of arylamino group is likely to be comparable with the basicity of the corresponding arylamines (p$K_\alpha$ of *p*-nitroaniline 1.02, of aniline, 4.58, of *p*-anisidine, 5.29 [5]), whereas the basicity of the pyrimidine ring apparently is close to the value established for pyrimidine (p$K_\alpha$ 1.3 [5]). These data show the direction of intermediate **B** protonation and consequently the readiness of arylamine elimination.

In reactions carried out without solvent or in aprotic solvent (toluene) no correlation was observed between p$K_\alpha$ of azoles(azines) and the products ratio due to the difference in the interaction mechanisms. Therefore to understand the results all the possible routes of these reactions should be considered (Scheme 2).

The reactions with low-basic aminoazoles **IV, VIa, VIb**, and **VIII** (p$K_\alpha$ 1.82–4.51, p$K_\alpha$ of the corresponding unsubstituted azoles 1.2–2.55) in the absence of protonic solvents evidently proceed through intermediate **C** and consequently lead to the formation of (arylimino)-pyrimidines **V**.

The "abnormal" reactivity of 2-amino-5-R-pyridines probably originates from the fact that they are bases of moderate strength (p$K_\alpha$ of pyridine 5.23) and in intermediate **D** the hydrogen of mercapto group is likely coordinated to the exocyclic nitrogen atom; the latter facilitates arylamine elimination and leads to the formation of pyrimidinethiones **III**.

The reaction products obtained from *N*-aryl-3-oxobutanethioamides with guanidine carbonate as seen from Table 1 were solely (4-arylimino)pyrimidines **V**. Inasmuch as guanidine is a strong base (p$K_\alpha$ 13.71 [5]), the reaction apparently proceeded through intermediate **E** where the guanidine served as a proton-acceptor. Thus the acid medium favors the arylamines elimination and the pyrimidinethiones formation whereas the presence of strong bases facilitates the ejection of hydrogen sulfide and the generation of (arylimino)pyrimidines.

The effect of the character of substituents in the phenyl ring of *N*-aryl-3-oxobutanethioamide is well consistent with the above rules: in reactions proceeding in AcOH the yield of pyrimidinethione is the greater the higher is the electron-donor effect of the substituent whereas in the absence of the protonizing solvent the thione is not formed (Table 2). Evidently the condensation in AcOH proceeds through intermediate **B**, and in the second case, via intermediate **C**.

Thus the reaction of *N*-aryl-3-oxobutanethioamides with 2-aminoazoles(azines) results in formation of derivatives of (arylimino)pyrimidines or pyrimidinethiones whose ratio depends on the heterocycle basicity in the initial 2-aminoazoles(azines), on the character of the substituent in the phenyl ring of thioamide, and on the protonating capability of the solvent.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a spectrometer Varian 300 (300 MHz) from solutions in DMSO-$d_6$ using TMS as internal reference.

**2-Methyl-7-R-4*H*-pyrido[1,2-*a*]pyrimidine-4-thiones IIIa and IIIb, 4-arylimino-2-methyl-4*H*-benzo-[4,5]thiazolo[3,2-*a*]pyrimidines Va–Vd, 5-**

**arylimino-7-methyl-2-R-[1,2,4]triazolo[1,5-*a*]pyrimidines VIIa–VIIc, and 7-methyl-5-phenyliminotetrazolo[1,5-*a*]pyrimidine (IX). General procedure**. A mixture of 5 mmol of *N*-aryl-3-oxobutanethioamide **Ia–Ie** and 5 mmol of 2-amino-5-R-pyridine (2-aminoazole) **IIa**, **IIb, IV, VIa, VIb**, and **VIII** was heated for 1–2 h at 120°C (bath temperature), cooled, diluted with 8 ml of ethyl ether, and the precipitate was filtered off.

**2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione (IIIa)**. Yield 0.414 g (47%), mp 156–158°C (from ACOH) (156–158°C [2]). $^1$H NMR and IR spectra are identical to those published in [2]. Found, %: C 61.18; H 4.83; N 15.71. $C_9H_8N_2S$. Calculated, %: C 61.34; H 4.58; N 15.90.

**2,7-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione (IIIb)**. Yield 0.409 g (43%), mp 140–142°C (from ethanol) (140–142°C [2]). $^1$H NMR and IR spectra are identical to those published in [2]. Found, %: C 63.40; H 5.11; N 14.88. $C_{10}H_{10}N_2S$. Calculated, %: C 63.13; H 5.30; N 14.72.

**2-Methyl-4-phenylimino-4*H*-benzo[4,5]thiazolo-[3,2-*a*]pyrimidine (Va)**. Yield 0.858 g (59%), mp 198–199°C (from DMSO) (198–199°C [3]). $^1$H NMR and IR spectra are identical to those published in [3]. Found, %: C 70.30; H 4.76; N 14.21. $C_{17}H_{13}N_3S$. Calculated, %: C 70.08; H 4.50; N 14.42.

**2-Methyl-4-(4-methoxyphenyl)imino-4*H*-benzo-[4,5]thiazolo[3,2-*a*]pyrimidine (Vb)**. Yield 0.770 g (48%), mp 186–187°C (from $CH_3NO_2$). $^1$H NMR spectrum, δ, ppm: 2.08 s (3H, 2-$CH_3$), 3.82 s (3H, $CH_3O$), 6.03 s (1H, H$^3$), 6.77 d (2H, *p*-$C_6H_4$, *J* 8.7 Hz), 6.90 d (2H, *p*-$C_6H_4$, *J* 8.7 Hz), 7.45 m ($2H_{arom}$), 7.90 m ($1H_{arom}$), 9.36 m ($1H_{arom}$). Found, %: C 67.49; H 4.56; N 12.81. $C_{18}H_{15}N_3OS$. Calculated, %: C 67.27; H 4.70; N 13.07.

**2-Methyl-4-(4-methylphenyl)imino-4*H*-benzo-[4,5]thiazolo[3,2-*a*]pyrimidine (Vc)**. Yield 0.793 g (52%), mp 177–179°C (from $CH_3NO_2$). $^1$H NMR spectrum, δ, ppm: 2.08 s (3H, 2-$CH_3$), 2.31 s (3H, $CH_3$), 5.99 s (1H, H$^3$), 6.76 d (2H, *p*-$C_6H_4$, *J* 8.1 Hz), 7.14 d (2H, *p*-$C_6H_4$, *J* 8.1 Hz), 7.46 m ($2H_{arom}$), 7.91 m ($1H_{arom}$), 9.34 m ($1H_{arom}$). Found, %: C 71.02; H 5.17; N 13.89. $C_{18}H_{15}N_3S$. Calculated, %: C 70.79; H 4.95; N 13.76.

**2-Methyl-4-[3-(trifluoromethyl)phenyl]imino-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine (Vd)**. Yield 0.987 g (55%), mp 189–191°C (from $CH_3NO_2$). $^1$H NMR spectrum, δ, ppm: 2.13 s (3H, 2-$CH_3$), 6.00 s (1H, H$^3$), 7.17 m ($2H_{arom}$), 7.34 m ($1H_{arom}$), 7.51–7.58 m ($3H_{arom}$), 7.95 m ($1H_{arom}$), 9.33 m ($1H_{arom}$). Found, %: C 59.89; H 3.48; N 11.77. $C_{18}H_{12}F_3N_3S$. Calculated, %: C 60.16; H 3.37; N 11.69.

**7-Methyl-5-phenylamino[1,2,4]triazolo[1,5-*a*]-pyrimidine (VIIa)**. Yield 0.698 g (62%), mp 183–185°C (from 2-propanol) (183–185°C [1]). $^1$H NMR spectrum is identical to that published in [1]. Found, %: C 64.20; H 5.11; N 31.29. $C_{12}H_{11}N_5$. Calculated, %: C 63.99; H 4.92; N 31.09.

**7-Methyl-2-methylsulfanyl-5-[3-(trifluoromethyl)-phenyl]amino[1,2,4]triazolo[1,5-*a*]pyrimidine (VIIb)**. Yield 0.898 g (53%), mp 198–200°C (from $CH_3NO_2$). $^1$H NMR spectrum, δ, ppm: 2.42 s (3H, 7-$CH_3$), 2.68 s (3H, SMe), 6.42 s (1H, H$^6$), 7.60 m ($1H_{arom}$), 7.69 m ($1H_{arom}$), 7.75 m ($2H_{arom}$), 10.22 s (1H, NH). Found, %: C 49.72; H 3.81; N 20.42. $C_{14}H_{12}F_3N_5S$. Calculated, %: C 49.55; H 3.56; N 20.64.

**7-Methyl-2-methylsulfanyl-5-(3-chlorophenyl)-amino[1,2,4]triazolo[1,5-*a*]pyrimidine (VIIc)**. Yield 0.905 g (57%), mp 191–193°C (from $CH_3NO_2$). $^1$H NMR spectrum, δ, ppm: 2.41 s (3H, 7-$CH_3$), 2.67 s (3H, SMe), 6.41 s (1H, H$^6$), 7.31 m ($1H_{arom}$), 7.37–7.49 m ($3H_{arom}$), 10.12 s (1H, NH). Found, %: C 50.93; H 4.09; N 23.15. $C_{13}H_{12}ClN_5S$. Calculated, %: C 51.06; H 3.96; N 22.90.

**7-Methyl-5-phenylaminotetrazolo[1,5-*a*]pyrimidine (IX)**. Yield 0.633 g (56%), mp 223–226°C (from $CH_3NO_2$). $^1$H NMR spectrum, δ, ppm: 2.76 s (3H, 7-$CH_3$), 6.70 s (1H, H$^6$), 7.11 m ($1H_{arom}$), 7.39 m ($2H_{arom}$), 7.83 m ($2H_{arom}$), 10.28 s (1H, NH). Found, %: C 58.64; H 4.19; N 36.94. $C_{11}H_{10}N_6$. Calculated, %: C 58.40; H 4.45; N 37.15.

Reactions of *N*-aryl-3-oxobutanethioamides **Ia, Ib**, and **Id** with 2-aminobenzothiazole (**IV**) in AcOH and isolation of the products were performed by procedure [3].

## REFERENCES


1. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., Chernega, A.N., Lozinskii, M.O., *Zh. Org. Khim.,* 2006, vol. 42, p. 1529.
2. Britsun, V.N., Borisevich, A.N., Pirozhenko, V.V., Lozinskii, M.O., *Zh. Org. Khim.,* 2007, vol. 43, p. 283.
3. Britsun, V.N., Borisevich, A.N., Esipenko, A.N., Lozinskii, M.O., *Zh. Org. Khim.,* 2007, vol. 43, p. 99.
4. Britsun, V.N., Borisevich, A.N., Lozinskii, M.O., *Zh. Org. Khim.,* 2007, vol. 43, p. 908.
5. *Spravochnik khimika* (Chemist's Handbook), Moscow: Khimiya, 1964, vol. 3, p. 81.

6. Gauptman, Z., Grefe, Yu., and Remane, Kh., *Organicheskaya khimiya* (Organic Chemistry), Moscow: Khimiya, 1979, p. 52.
7. Karapet'yants, M.Kh., *Vvedenie v teoriyu khimicheskikh protsessov* (Intraduction to Theory of Chemical Processes), Moscow: Vysshaya Shkola, 1981, p. 20.
8. March, J., *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, New York: Wiley-Interscience, 1985.
9. Albert, A., Goldacre, R., and Phillips, J., *J. Chem. Soc.*, 1948, 2, p. 2240.
10. Schofield, K., Grimmet, M.R., and Keene, B.R., *Heteroaromatic Nitrogen Compounds – The Azoles*, Cambridge Univ. Press, 1976, p. 284.